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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,887	12/11/2001	Geoffrey W. Krissansen	87792.353006	2382

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
04/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/014,887	KRISSANSEN ET AL.	
	Examiner	Art Unit	
	LEI YAO	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10-15,18-23,26-31,34-39 and 42-47* is/are pending in the application.

4a) Of the above claim(s) *10,11,15,18,19,23,26,27,31,34,35,39,42,43 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12-14,20-22,28-30,36-38,44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendment and Arguments

The Amendment filed on 2/11/2008 in response to the previous Non-Final Office Action (10/9/2007) is acknowledged and has been entered.

Claims 1-4, 10-15, 18-23, 26-31, 34-39 and 42-47 are pending.

Claims 10, 11, 15, 18, 19, 23, 26, 27, 31, 34, 35, 39, 42, 43 and 47 are currently withdrawn for non-elected invention.

Claims 1-4, 12-14, 20-22, 28-30, 36-38, 44-46 are under consideration.

Clarification

On page 1 of the remarks dated 2/11/2008, applicant states

"the Rejection of The Claims Under 35 U.S.C. § 112, First Paragraph As Lacking Adequate Enablement Must Be Withdrawn"

It is noted that there is no rejection made under 35 U.S.C. § 112, 1st Paragraph-enablement in the last Office action dated 10/9/2007.

Rejections Withdrawn

The rejections of claims 3, 4, 28-30, 36-38, and 44-46 are rejected under 35 U.S.C. 112 second paragraph as being indefinite are withdrawn in view of amendment to the claims and applicant's argument.

Response to Amendment and Arguments

Claim Rejections - 35 USC § 103

Claims 1-4, 12-14, 20-22, 28-30, 36-38, and 44-46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Futami et al., (J of Immunotherapy, vol 12, 247-255, 1992) in view of Wilson et al., (Int. J. Radiation Oncology Biol. Phys., Vol. 42, page 905-908, 1998) and Olsson et al., (International Immunology, vol 10, page 499-506, 1998), which is reiterated as the following:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The claims are drawn to methods of treating a patient with advanced or large tumor comprising administering CAM (B7.1) in conjunction with tumor restricted agent DMXAA (claims 1 and 2) or potentiate the activity of tumor restricted agent DMXAA or CAM (B7.1) comprising administering CAM (B7.1), CD80 antigen, or tumor restricted agent DMXXA (claims 3 and 4) in combination with immunotherapeutic agent to eradicate an advanced or large tumors present in a patient, wherein CAM is administered prior to from 12-48 hours the tumor restricted agent DMXXA (claims 12-13, 20-21, 28-29, 36-37, 44-45), wherein the method further includes the administering of an addition tumor growth-restricting agent (claims 14, 22, 30, 38, 46).

Futami et al., teach a method of treating a tumor by 5-methyl XAA in conjunction with a T-cell stimulating molecule, IL-2. Futami et al., teach that the activities of XAA analogs can be potentiated by recombinant IL-2 in treating a tumor by showing the synergistic effect in combination (page 251, col 2). Futami et al., teach a method of treating cancer by administering a subject both reagents or administrating two reagent at different time (page 249, column 1-2 and page 251, column 1). Futami et al., also teach the analogs of XAA alone or IL-2 alone is not as effective as combined therapy for treating mice bearing a tumor (figure 2-4).

Futami et al., do not teach that treating cancer with specific analog of XAA, DMXAA (5, 6, dimethyl anthenone-4-acetic acid (XAA)) in conjunction with CAM, B7.1.

Wilson et al., teach 5, 6-dimethyl anthenone-4-acetic acid (DMXAA), which potentiates tumor radiation response compared to each treatment alone (entire reference, especially, page 906, col 2, page 907, tables). Wilson et al., teach the treatment commenced established tumor when tumors reach to 0.4-

0.6g (page 96, col line 5-8 from bottom). Wilson et al., also teach that DMXAA induces synthesis of TNF, an anti-tumor agent production (abstract).

Olsson et al., teach that Human IL-2 is induced by CD80 (B7.1, a CAM molecule) in cancer cells and T cells (entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to replace the IL-2 with its stimulator (CAM) and a specific analog of XAA, DMXAA with a expected result. One of ordinary skill in the art at the time the invention was made would have been motivated to apply the teachings of Wilson et al., and Olsson et al., to the method of Futami et al., in order to benefit for the treatment of advanced or large tumor because both Wilson et al., and Futami have already shown the advantage of the tumor therapy by potentiating or synergistic response for the large tumor in combination of anti-tumor treatment with DMXAA and because Olsson et al., show the association between T cell growth factor IL-2 and B7.1 stimulation. One of ordinary skill in the art at the time the invention was made would have been motivated with reasonable expectation of success to modify the treatment schedule or method steps in order to optimize and increase the efficacy of the treatment by administering B7.1 prior to the DMXAA because Futami et al., have already shown administering a subject two or more reagents at different times and Olsson et al., teach that T-cell proliferation stimulated by IL-2 is induced by B7.1 and Wilson et al., also show that DMXAA induces other antitumor cytokine productions during the treatment, which would suggest the combination treatment results from more than two anti-tumor agents presented in the subject. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Previous response to applicant's argument dated 7/16/2007 is also maintained for the reason of record as set forth in the Office action dated 10/9/2007 (page 5-8).

The response filed 2/11/2008 has been carefully considered but is deemed not to be persuasive. Applicant argues the prosecution process for the citation of the reference (points 1-4, page 10-11) stating that the Office should have produced any reference providing DMXAA (5, 6 dimethyl XAA) and

specifically reference of DMXAA by Wilson earlier in the prosecution to save the fee and patent term. In response, looking back the persecution history applicant merely provides the part of the history starting from the final rejection (1/16/2007), in which the Office maintains the 103 rejection for the claims amended by adding the DMXAA, the analog of XAA, in the base claim as the tumor restricted agent. The rejection is remained based on the teachings of Futami on a method of treating cancer with 5-Methyl XAA combined with IL-2, which is induced by CAM (Olsoon). 5, 6 dimethyl XAA (DMXAA) is an analogs of 5-methyl XAA with additional methyl at position 6. Futami not only self, but also cites references (13, 20 and 21) that teach and suggest the importance of position 5 and 6 of methyl in XAA derivatives for the anticancer activity, which would suggest one skilled in the art to use the known compound 5, 6 dimethyl XAA with reasonable expectation of success in cancer treatment. When the RCE is filed later on 7/16/2007 and applicant still argues the 103 rejection by the references of Futamin and Olsoon et al. The Office considered that it is good time to add the reference of Wilson et al., who clearly teach the anticancer activity of 5, 6 dimethyl XAA (DMXAA), which would make the rejection for the amended base claims reciting DMXAA stronger and clearer.

> Applicant further argues (point 5, page 12):
>
> 5. Wilson Teaches DMXAA, But Does NOT Teach IL-2, and Therefore CANNOT Be Used To Fit The Examiner's Logic Nor To Replace That Which Is Already Absent In Futami
>
> There MUST be one reference that teaches DMXAA and IL-2, and another reference that teaches CAM B7.1 giving rise to IL-2.
>
> With regard to Wilson, Applicants state uncategorically that this reference similarly does not provide both DMXAA and IL-2, and therefore no more satisfies the Examiner's logic than did Futami or Olsson. Thus the Examiner states in the Office Action that DMXAA is used in combination with radiation therapy, which is certainly not the combination of agents used in the present invention. And, although the Examiner also states that "Wilson et al. also teach that DMXAA induces synthesis of TNF" (Office Action page 4), TNF is irrelevant to the Examiner's claim of the combination of Futami + Olsson + Wilson, since the link to CAM B7.1 is, according to the Examiner, the result of this CAM's involvement in IL-2 expression, as taught in Olsson.

In response, first, applicant is reminded that the references are relied upon in combination and are not meant to be considered separately in the rejection under 35 U.S.C. 103(a) as given in the guideline of MPEP 2141, particularly, MPEP 2141.02:

> **In determining the difference between the prior art and the claims, the question under 35 USC103 is not whether the difference themselves would have been obvious, but whether the claimed invention as a whole would have been obvious.**

and

> **it is improper to argue and discuss the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981).**

Accordingly, it is improper for applicant to argue and discuss Wilson reference individually without clearly addressing the combined teachings. As stated in the rejection, Futami and Olsoon teaches the method of treating cancer with CAM and 5-methyl XAA. Futami teaches the importance of methyl at position 5 of XAA and cite references teaching the anticancer activity of 5' and/or 6' methyl of XAA derivatives, for example, reference 21. Wilson explicitly and specifically teaches the DMXAA for cancer treatment. Based on the guideline of MPEP above, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to replace 5-methyl XAA with another analog DMXAA that has been used as a tumor restricted agent in the art based on the suggestion of Futami and would be motivated to do so with reasonable expectation of success for the claimed method. Second, regarding the teaching of Wilson on induction TNF by DMXAA, the Office just extends the teaching of Wilson on the mechanism of the DMXAA for the tumor treatment, which is not directly related with IL-2 or CAM (B7.1) recited in the method. As stated above by applicant, the CAM's involvement in IL-2 expression is taught in Olsson.

Applicant in point 6 of page 13-14 further argues,

> 6. The Examiner's Own Statements Regarding Unpredictability Defeat Any Claim On The Examiner's Part Of A Prima Facie Case Of Obviousness

Applicant cites the scope of enablement rejection made in the earlier Office Action dated 8/23/06:

> One skilled in the art recognizes that the search for combinations of drugs (each has less effect when it is used alone) exerting a combined effect requires a great deal of empirical testing of agents known to have anti-cancer properties or that may augment an agent having anti- cancer properties (Gerson et al, WO03/070234, page 2, lines 11-14). In addition, not all the analogue of XAA has a tumor restricted function, Futami et al., (J of Immunotherapy, vol 12,247-255) indicates that 7- methyl-XAA, a analogue of XAA, self, or combination with IL-2 has not synergistic activity in suppression of tumor growth (page 252-253, col 1). Thus, it would be undue

> experimentation to test two agents in combination in order to determine whether one skilled in the art could use them together for treating a large or advanced tumor.

and then states.

> Examiner believes that there is no reasonable expectation of success in combining different drugs, how can the Examiner possibly claim that such expectation of success exists for combining the disparate and non- relating results for different compounds of the TRIPLE combination of Futami + Olsson + Wilson?

In response, first, the argument is invalid because there is NO enablement rejection made for the amended claims (7/16/2007) in the last Office action dated 10/9/2007; Second, if the argument is considered, Applicant is reminded that the scope of enablement rejection made in the Office action dated 8/23/2006 is for the claims reciting a method of treating advanced or large tumor with any analogue of XAA in combination with any CAM and again, Applicant is reminded that in this rejection, the Office clearly states that the disclosure is enabled for the claimed method of using DMXAA in combination with CAM, B7.1, that induces expression of IL-2. As stated in the argument above, the Office action cites a reference indicating some of XAA analog does not enhance the anticancer activity in combination with IL-2. Thus, Applicant's argument is not persuasive either.

> Applicant further argues in point 7 of page 14,
>
> 7. The Examiner Appears To Misunderstand The Results Of Futami
>
> The Examiner is confused as to the results of Futami, since the Examiner continues to assert that Futami teaches DMXAA, when in fact it does not.

In response, in any of the Office actions comprising the last action dated 10/9/2007, the Office only states that Futami teaches 5-methyl XAA or analogs of XAA, not DMXAA, that has the chemical name 5, 6-dimethyl anthenone-4-acetic acid (XAA) as evidenced by Wilson et al., above. The Applicant seems confused the 5-methyl XAA with 5, 6-dimethyl XAA although both have the same anticancer activity. Therefore, the rejection is reiterated above.

> Applicant further argues in point 8 of page 14,
>
> 8. The Examiner's Argument Constitutes Impermissible Hindsight
>
> In the present Office Action the Examiner has added a reference (Wilson) to the two previously

> cited (Futami and Olsson), and argued that all three of these references in combination render the currently pending claims obvious. In light of the above discussions, it is clear that the Examiner has obtained these three references for combination based on an impermissible hindsight analysis, specifically an analysis in which an endpoint - DMXAA and the CAM B7.1 - leads to the identification of the references, and not vice-versa.

In response, the definition of hindsight as: *perception of the nature of an event after it has happened*. The references by Futami (1992) teaching on the anticancer activity of analogs of DMXAA in combination of IL-2 with Wilson (1998) on the same activity of DMXAA are published before the current application filed on year 2000 and claiming the priority to year 1999. The teaching IL-2 is induced by CAM (7.1) by Olsson is also published in 1998, before the application filed. These publications observed the nature of the anti-cancer activity of XAA analogs comprising DMXAA. Thus, the claimed invention would be obvious over the references in combination and one skilled in the art would arrive the claimed invention with expected result as stated in *In re Kerkhoven*:

> It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art." SEE *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) and MPEP 2144.06.

Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for the reasons of the record.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643

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	10/014,887	KRISSANSEN ET AL.	
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	LEI YAO	1642	